

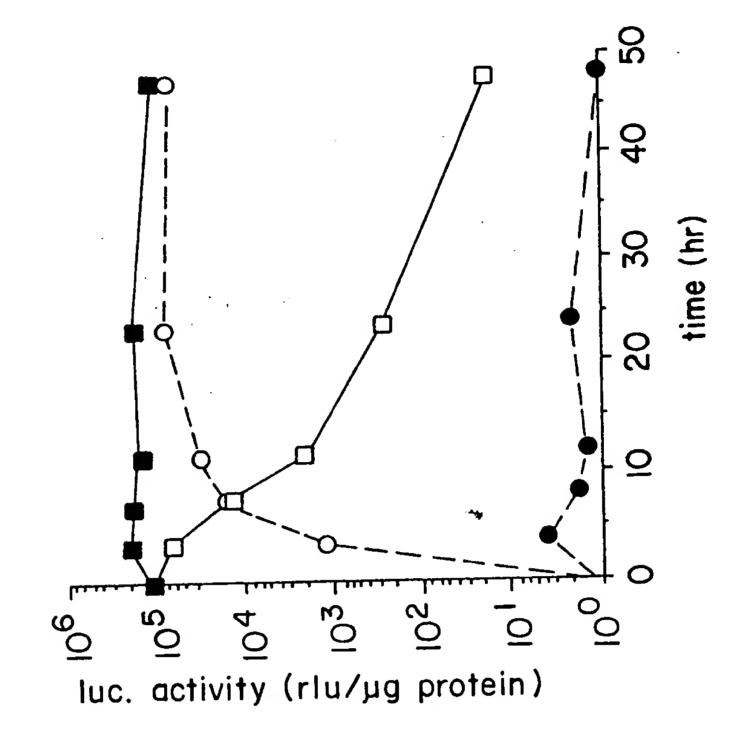


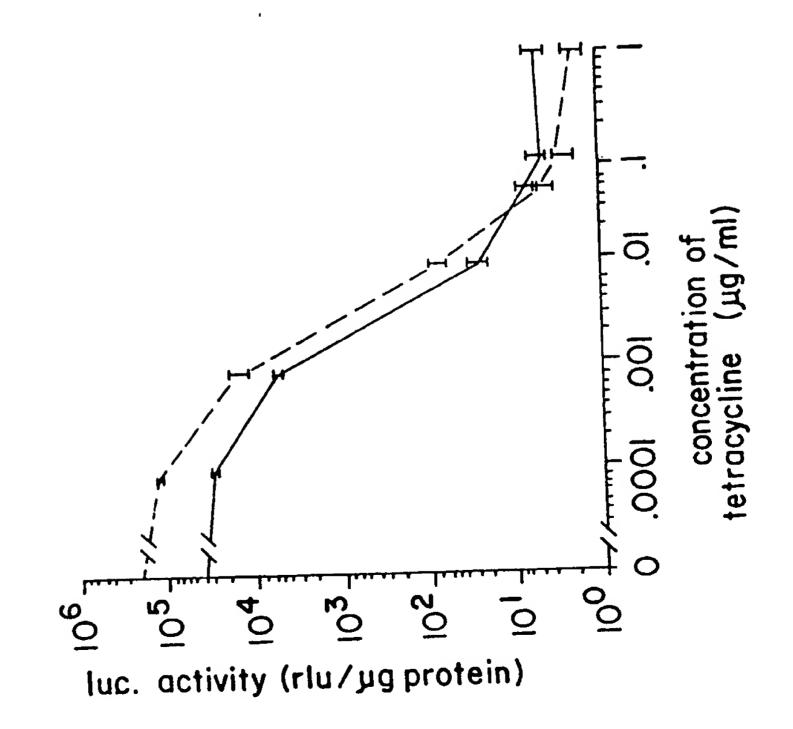
FIG. 2A

FIG. 2B

F16.3A

F16.3B





TO SUBJECT AS

Asn AGC GCA TTA GAG CTG CTT AAT Leu Leu Glu Ala Leu Ser Asn ATT AAC Ile GTG Val Lys AGT Ser AAA Arg Leu Asp Lys ATG TCT AGA TTA GAT Met Ser

GTA Val Leu Gly CTA GGT AAG Gln Lys GCC CAG Arg Lys Leu Ala CGT AAA CTC Thr Thr ACA ACC Len GTC GGA ATC GAA GGT TTA G1yGlu Ile GlyVal Glu

AAA AAT AAG CGG GCT TTG CTC GAC GCC Ala Leu Asp Len Ala Arg Asn Lys Lys GTA Val His CAT Trp TGG Leu Tyr CAG CCT ACA TTG TAT Gln Pro Thr Glu GAG

Leu Glu Gly TGC CCT TTA GAA GGG Pro Cys TTTPhe ACT CAC His Thr CAT Arg His His AGG CAC TTA GCC ATT GAG ATG TTA GAT Leu Asp Glu Met Ile Ala Leu AAT AAG GCT AAA AGT TTT AGA TGT GCT TTA Cys Ala Leu Phe Arg Ser Lys Ala Asn Lys CGI Arg TTT TTA Len Phe AGC TGG CAA GAT Trp Gln Asp Ser GAA Glu

Fig. 4A

TTA GGT ACA CGG CCT ACA GAA AAA Thr Glu Lys Gly Thr Arg Pro Len CAT Val His AAA GTA Lys GCA Ala His Arg Asp Gly GAT GGA CGC CAT Ser AGT CTALen

TCA Ser TTTPhe Gln Gly TTT TTA TGC CAA CAA GGT Phe Leu Cys Gln Gln Leu Ala CAA TTA GCC Glu Asn TAT GAA ACT CTC GAA AAT Tyr Glu Thr Leu Gln CAG

 $\mathbf{I}\mathbf{G}\mathbf{C}$ Gly Cys AGC GCT GTG GGG CAT TTT ACT TTA GGT Phe Thr Leu Gly His Val Ala Ser CTCLen Tyr Ala AAT GCA TTA TAT GCA Leu Glu Asn Ala GAG CTA Len

 Thr GAA ACA CCT ACT Thr Pro Glu Glu Glu Arg GCT AAA GAA GAA AGG Ala Lys GIC Val Gln CAA His CAT Glu Asp Gln Glu GTA TTG GAA GAT CAA GAG Leu Val

Gln TTA CGA CAA GCT ATC GAA TTA TTT GAT CAC CAA Asp His Phe Ile Glu Leu Leu Arg Gln Ala Len ATG CCG CCA TTA Pro Met Pro Ser ACT GAT AGT Asp Thr

Fig. 4B

GAA TTG ATC ATA TGC GGA TTA GAA Leu Glu Cys Gly Ile Glu Leu Ile Leu CTTG1yGGC Phe TTCLen GCC TTC TTA Phe Ala CCA Ala Glu Pro GCA GAG Gly GGT

AAC Ala Arg Thr Lys Asn AAA CGT ACG GCG Ser Arg AGC CGC TyrTAC Ala GCG Ser ICC G1yGGG CAA CTT AAA TGT GAA AGT Glu Ser Leu Lys Cys Gln Lys AAA

Pro CTC GAT CTC CCG GAC GAC GAC GCC CCC Pro Asp Asp Asp Ala Len Leu Asp CIGLen G1yGGC Glu GAG ATC Ile Thr GGG TCT ACC Gly Ser TAC TyrAAT Asn

ACG Thr Gly His GGA CAC Leu Pro Ala CIC CCC GCG TTTPhe Ser CIG ICC Leu CGC Arg Pro CCG GAA GAG GCG GGG CTG GCG GCT Ala Gly Leu Ala Ala Glu Glu

CAC His CCG ACC GAT GTC AGC CTG GGG GAC GAG CTC Leu Gly Asp Glu Leu Ser Asp Val Thr Pro CCC Pro GCC Ala Ser Thr CGC AGA CTG TCG ACG Leu Arg Arg

Fig. 4C

RASTVIA

SA SUDOLAS

Asp CTA GAC GAT TTC GAT Phe Asp Leu Asp GCC GAC GCG Ala Asp Ala His CAT Ala GCG Met ATG B C C Ala TTA GAC GGC GAG GAC GTG Leu Asp Gly Glu Asp Val

Asp CCC CAC GAC His Pro Phe Thr TTT ACC Ser Pro Gly Pro Gly CCG GGA GGT TCC CCG GAT Asp GlyGAC ATG TTG GGG GAC GGG Asp Asp Met Leu Gly CIG Leu

GAC TTC GAG TTT GAG CAG ATG TTT Glu Gln Met Phe Phe Glu Asp Phe Ala ATG GCC Asp Met GAT Leu CIG Ala GCC CCC TAC GGC GCT Pro Tyr Gly Ala Ser ICC

TAC GGT GGG TAG Tyr Gly Gly Glu GAG ACC GAT CCC CTT GGA ATT GAC Asp Pro Leu Gly Ile Asp Thr

Fig. 4D

Asn CTT AAT Leu AAC AGC GCA TTA GAG CTG Len Glu Len Ala Asn Ser ATT Ile GIG Val Lys Ser AGT AAA LysAsp AGA TTA GAT Arg Leu $_{
m LCI}$ Ser ATG Met GTA Val G1yGGT AAG CTA Glu Lys Leu CAG Thr Arg Lys Leu Ala AAA CTC GCC ACC CGT ACA \mathtt{Thr} Leu GGA ATC GAA GGT TTA GlyGlu Ile G1yVal GIC Glu GAG

AAA AAT AAG CGG GCT TTG CTC GAC GCC Asp Ala Leu Leu Ala Arg Lys Asn Lys GTA Val His TGG Trp Tyr CCT ACA TTG TAT Pro Thr Leu GAG CAG Glu Gln

999 G1yLeu Glu CCT TTA GAA Pro TIT IGC Phe Cys CAC His \mathtt{Thr} CAT ACT His CAC Arg His AGG Asp TTA GCC ATT GAG ATG TTA GAT Leu Clu Met Ile Ala Len

TTALeu CGT AAT AAC GCT AAA AGT TIT AGA TGT GCT Lys Ser Phe Arg Cys Ala Ala Asn Asn Arg Leu TTT TTA Phe GAA AGC TGG CAA GAT Ser Trp Gln Asp Glu

Fig. 5A

CAT TTA GGT ACA CGG CCT ACA GAA AAA Pro Thr Glu Lys Thr Arg G1yLeu His GTA Val Lys Ala CGC GAT GGA GCA Arg Asp Gly CAT His CTA AGT Leu Ser

TCA Ser TTTGly Phe GGT CAA Gln Cys Gln TGC CAA TTALeu TTTPhe GCC Ala TTA Gln Leu CAA Asn CAG TAT GAA ACT CTC GAA AAT Tyr Glu Thr Leu Glu Gln

JBL CysThr Leu Gly GCT GTG GGG CAT TTT ACT TTA GGT Phe His Gly Val Ala Ser CTC AGC Leu GCA Ala $\mathtt{T}\mathtt{yr}$ GAG AAT GCA TTA TAT Len Ala Glu Asn Leu

Thr GCT AAA GAA GAA AGG GAA ACA CCT ACT Pro Arg Glu Thr Glu Lys Glu Ala CAA GTC Gln Val GTA TTG GAA GAT CAA GAG CAT Leu Glu Asp Gln Glu His Val

CAC CAA Asp His Gln GAT GAT AGT ATG CCG CCA TTA TTA CGA CAA GCT ATC GAA TTA TTT Glu Leu Phe Arg Gln Ala Ile Leu Leu Pro Pro Ser Met Asp ACT Thr

Fig. 5B

Glu CTT GAA TTG ATC ATA TGC GGA TTA GAA Leu Gly Cys Ile Ile Len Glu Leu Sec GlyTIC Phe Len GGT GCA GAG CCA GCC TTC TTA Phe Ala Pro Glu Ala G1y CTGLeu AGA Arg Arg CGC \mathtt{Thr} ACG His ATA CAC Ile Ser TCG GAT CCA Asp Pro $_{
m LCL}$ Ser G1y999 GAA AGT Glu Ser \mathtt{TGT} Cys CAA CTT AAA Gln Leu Lys AAA Lys

G1yGAC GAG CTC CAC TTA GAC GGC Leu Asp His Glu Leu Asp CTG GGG Leu Gly AGC Ser GIC Val Asp CCC CCG ACC GAT Thr Pro Pro CCC Ala ACG Thr TCG Ser

AŢĠ Met Leu Asp CTG GAC Asp GAT Phe GAT TTC Asp Asp GAC CTA Len Ala BCB Asp GAC GCC Ala His CAT GCG Ala GAG GAC GTG GCG ATG Ala Met Asp Val Glu

Pro GGT CCG GGA TIT ACC CCC CAC GAC TCC GCC CCC Ser Ala Asp Pro His \mathtt{Thr} Phe Gly Pro GlyPro GAC GGG GAT TCC CCG Ser Gly Asp Asp GGG GlyTTG

Fig. 5C

TIT GAG CAG ATG TIT ACC GAT GCC Thr Asp Ala Asp Phe Glu Phe Glu Gln Met Phe GAC TTC GAG Tyr Gly Ala Leu Asp Met Ala GAT ATG GCC CIG TAC GGC GCT

CTT GGA ATT GAC GAG TAC GGT GGG TTC TAG Leu Gly Ile Asp Glu Tyr Gly Gly Phe * Fig 5D

DRAFIE

CTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACACCGGGACCGATCCAGCCTCCGC CGAGTAGGCGTGGGAGGCC<u>TATATAG</u>CCAGAGCTCGTTTAGTGAACCGTCAGATCGC AAGTCGAGTTACCCCTATCAGTGATAGAGAAAAGTGAAAGTCGAGCTCGGTACCCGGGT GAAAGTCGAGTTTACCCTCTCTCAGTGATAGAGAAAAGTGAAAGTCGAGTTTACCACTCCC TATCAGTGATAGAGAAAGTCGAGTTTACCACTCCCTATCAGTGATAGAAAATGTGA CCTATCAGTGATAGAGAAGTCGAGTTTACCACTCCCTATCAGTGATAGAAAAGT GAATTCCTCGAGTTTCCCCTATCAGTGATGAAAAGTGAAAGTCGAGTTTACCACTC

Fig. 6

9

CTGGAGACGCCATCCACGCTGTTTTGACCTCCATAGAAGACACCGGGACCGATCCAGCCTCCGC CGAGTAGGCGTGGGGGCCCTATATAAGCAGAGCTCGTTTAGTGAACCGTCAGATCGC ATCACTGATAGGGAGTGGTAACTCGACTTTTCACTTTTCTCTATCACTGATAGGGAGTGGTAAA GAATTCCTCGACCCGGGGTACCTCTTCACTTTTCTCTCTATCACTGATAGGGAGTGGTA

Fig. 7

C C DRAF (CH)

TCGACTTTCACTTTTCACTGATAGGGAGTGGTAAACTCGAGATCCGGCGAATTCGAAC CGGTCCGAGGTCCACTTCGCATATTAAGGTGACGCGTGTGG TCACTGATAGGGAGTGGTAAACTCGACTTTCACTTTTTCTCTATCACTGGGAGTGGTAAAC ACTCGACTTTCACTTTTCTCTCTGATAGGGAGTGGTAAACTCGACTTTCACTTTTCTCTA TATCACTGATAGGGAGTGGTAAACTCGACTTTCACTTTTCTCTCTATCACTGGGAGTGGTAA GAGCTCGACTTTCACTTTTCTCTCTGATAGGGAGTGGTAAACTCGACTTTCACTTTTTTT ACGCAGATGCAGTCGGGGGGGGGG CCTCGAACACCGAG

Fig. 8

AGGGGAGCCAGACCTCAGAGGCCTCGTCTCTCCCCCATCTCCCTGGACGGTT GGCGCCCTCCCCACCGAGGTCGCATCCCAGCTCCTGGGTCGCCCGGACCCTGGCCCTTCC GGGAGTTCACATGACTGAGCTGAAGGCAAAGGAACCTCGGGCTCCCCACGTGCGGGC TATATCCCGGCACCCCTCCTAGCCCTTTCCCTCCTCCGAGAGACGGGGGGAGAAAAG TCCAGGAGGTGGAGTCCGGGGTCCAAACCCCACACCCATTTTCTCCTCCTTGCCCC GAATTCGAGCTCGGGCCCCCCCTCGAGGTCGACGGTATCGATAAGCTTGATATCGAAT ACGCCATCCACGCTGTTTGACCTCCATAGACACCGGGACCGATCCAGCCTCCGGCCCC GGCGTGTACGGAGGCCTATATAAGCAGAGCTCGTTTAGTGAACCGTCAGATCGCCTGGAG AGTTTACCACTCCCTATCAGTGAAAAGTGAAAGTCGAGCTCGGTACCCGGGTCGAGTA TGATAGAGAAAAGTCGAGTTTACCACTCCCTATCAGTGATAGAGAAAAGTCG CGAGTTTACCACTCCCTATCAGTGATAGTGAAAGTCGAATTTACCACTCCCTATCAG AGTGATAGAGAAAGTCGAGTTTACCACTCCCTATCAGTGATAGAGAAAAGTGAAAGT CTCGAGTTTACCACTCCCTATCAGTGATAAAAGTGAAAGTCGAGTTTACCACTCCCTATC

Fig. 9A

DRAFIUM

CTGGAGGGGAGACTACGACGGCGGGGCCGCCGCCAGC CGCTGGCCACCTGGGTGGATTTCATCCACGTGCCCATCCTGCCTCTCAACCACGCTTTCCT CGCTTCTCGGCGCCCAGGGTCTCCTTGGCGGAGCAGGACGCGCCGGTGGCGCCTGGCGCTCCC AGCTGCCCCCGCGCGCCGCCGCAGGAGGCGTCGCCTTGTCCCCCAAGGAAGATTCT GCACCGTGGGCCTGAAGGGCCCAACCTCGGGCACGAGGCACGGCGGCGGCGGAGGAGG GTGAAGCCATCCCGCTGCTGCAGGTAGACGAGGAGGACAGCTCCGAATCCGAGG CAGGGGACTGTCACCAGGCAGCTGCTCCCCTCCTCTGGGAGCCCTCACTGGCCCAA TGAGCCGACCAAGGCAGGCGACTCTGGGACGGCAGCCCCACAAGGTGCTGCC GGCCCCGACCTCCCCCCCCCCCCCCCCCCCCCTACCAAAGGGGTGTTGGCCCCCCTCA GGGTCCCGGGCCACCCTGCCACCTGCGAGGCCATCAGCCCGTGGTGTTTT CGAGACCTCCAGAAAAGGACAGCCTGCTGGACAGTGTCCTCGACACGCTCCTGGCCCTCT TTGTCAGACGTGGAGGCGCATTTTCCTGGAGTCGAAGCCCCGGAGGGGGGAGAGACAGCT GCTCTTCCCCCGGCCTGTCAGGGGCAGAACCCCCCAGAAGGAGGCAGGAAGACGCCCCCGTCG GGCCACCGCACCAGGCAGCTG

Fig. 9B

GCCGTGCTCAAGGACCCTGCCGCAGGTCTACACGCCCTATCTCAACTACCTGAGGCCGGATT GGCCGCCCTGCGCTCCGGCCTCGGCCTCAACGGACTCCCGCAACTCGGCTACCAGGCC CCGGCGCCTGCCTCCCGCGGGACGGCCTGCCCTCCACCTCCGCCTCGGGCGCGCAGCCGCGG CCAGGCAGTGCCTCCTCCTCGTCGTCGGGGTCGACCCTGGAGTGCATCCTGTAC CGCCACCTCGCTCGCCTCGTCCTCGTCCAGACCCGGGGAAGCGGGTGGCGCCTC CGTACGTACCTGGTGGTACCCCCCCCCCTTCCCGGACTTCCAGCTGGCAGCCGC CCAGCCGCCCCCTCAAGATAAGGAGGAAGAAGACCGCCGCGGCCGCGCGCCCCCG CCGACTGCACCTACCCCGACGCCCAAAGATGACGCGTTCCCCCTCTACGGCGACTT

Fig. 9C

AAAAGGGCAATGGGGCAGCATAACTATTTATGTGCTGGAAGAAATGACTGCATTGTTGATA

TGGGGATGAAGCATCAGGTCTTTATGGTGTCCTCACTGTGGGAGCTGTAAGGTCTTTT

DRAFTS:

TCACAAAACTTCTTGATAACTTGATCTTGTCAAACAACTTCACCTGTACTGAATAC CTCATCAAGGCAATTGGGTTTGAAAAAGGAGTTGTTTCCAGCTCACAGCGTTTCTATCAGC TCAAGCTTCAAGTTGCTTCCTCTGCATGAAGTATTACTACTTCTTAATACAAT CGGATGAAAGAATCATCATTCACTATGCCTTACCATGTGGCAGATACCGCAGGAGTTTG ATGACCAGATAACTCTCCAGTATTCTTGGATGATTAATGGTATTTGGACTAGGATGGAG CGGCAACTTCTTCAGTGGTAAATGGTCCAAATCTCTTCCAGGTTTTCGAAACTTACATATTG ACATGACAACACAAAGCCTGATACCTCCAGTTCTTTGCTGACGAGTCTTAATCAACTAGGCGAG TACAGTTAATTCCCCCCTCTAACCTGTTAATGAGCATTGAACCAGATGTGATCTATGCAGG CTCCCACAGCCAGTGGGCATTCCAAAGCCAACGAATCACTTTTTCCCAAGAGAGA TGGAGGGCGAAAATTAAAAGTTAAAGTCAGAGTCATGAGAGCACTCGATGCTGTTGCT AAATCCGCAGGAAAACTGCCCGGCGTGTCGCCTTAGAAAGTGCTGTCAAGCTGGCATGGTCCT

Fig. 9D

GAGGCAAGACTCGGGCGCCCTGCCCGTCCCAGGTCAACAGGCGGTAACCGGCCTCTTC CGACCAAGCTTGGCGAGATTTTCAGGAGCTAAGGAAAAAAATGGAGAAAAAAATCACTGGAT AAAGCAAGTAAAACCTCTACAAATGTGGTATGGCTGATTATGATCCTGCAAGCCTCGTCGTCTG CAGACATGATAAGATTGATGAGTTTGGACAAACCACACTAGAATGCAGTGAAAAAATG AGTTTTTATAATTCTGAAATTCCTGCAGCCCGGGGGATCCACTAGTTCTAGAGGATC TTATTTTTCAAAGAATTAAGTGTTGGTATGTCTTTTCGTTTTGGTCAGGATTATGACGTCTCG CAGTTACCCAAGATATTGGCAGGGATGGTGAAACCACTTCTTTCATAAAAAGTGAATGTCAA ATTTATCCAGTCCCGGCGCTGAGTGTTTGAATTTCCAGAAATGATGTCTGAAGTTATTGCTGCA

Fig. 9E

GCGAGGTATGTAGGCGGTGCTACAGAGTTCTTGAAGTGGTGGCCTAACTACGGCTACACTAGAA GTCCAACCCGGTAAGACACGACTTATCGCCACTGGCAGCCACTGGTAACAGGATTAGCAGA GCTGTGTGCACGAACCCCCCGTTCAGCCCGACCGCTGCGCCTTATCCGGTAACTATCGTCTTGA GCGCTTTCTCAATGCTCACGCTGTATCTCAGTTCGGTGTGTAGGTCGTTCGCTCCAAGCTGG CTCTCCTGTTCCGACCCTGCCGCTTACCGGATACCTGTCCGCCTTTCTCCCTTCGGGAAGCGTG GGTGGCGAAACCCGACAGACTALAAGATACCAGGCGTTTCCCCCCTGGAAGCTCCCTGGTGCG CTGGCGTTTTTCCATAGGCTCCCCCCCTGACGAGCATCACAAAATCGACGCTCAAGTCAGA TGCGGCGAGCGGTATCAGCTCACTCAAAGGCGGTAATACGGTTATCCACAGAATCAGGGGATAA CGCAGGAAAGAAATGTGAGCCAAAAAGGCCAAAAAGGCCAGGAACCGTAAAAAGGCCGCGTTG GGTTTGCGTATTGGGCGCTCTTCCGCTTCGCTCACTGACTCGCTGCGCTCGGTCGTTCGGC TCAATGTACCTATAACCAGACCGTTCAGCTGCATTAATGAATCGGCCAACGCGGGGGAGAGGC

Fig. 9F

GGACAGTATTTGGTATCTGCGCTCTGAAGCCAGTTACCTTCGGAAAAAAGAGTTGGTAGCTC

enza in t

TAGTGTATGCGGCGACCGGTTTGCCCCGGCGTCAATACGGGATAATACCGCGCCACATA TGTCATGCCATCCGTAAGATGCTTTTTCTGACTGGTGAGTACTCAACCAAGTCATTCTGAGAA TCAGAAGTAAGTTGGCCGCAGTGTTATCACTCATGGTTATGGCAGCACTGCATAATTCTTTAC CGAGTTACATGATCCCCCATGTTGCAAAAAAGCGGTTAGCTCCTTCGGTCCTCCGATCGTTG CATCGTGGTGTCGTCGTTTTGGTATGGCTTCAGTTCCGGTTCCCAACGATCAAGG GGGAAGCTAGAGTAGTTCGCCAGTTAATAGTTTGCGCAACGTTGTTGCCATTGCTACAGG AATGATACCGCGAGCTCCGGCTCCAGGTTTTATCAGCAATAAACCAGCCGGA CCTGACTCCCCGTGTAGATAACTACGAGAGGGGTTTACCATCTGGCCCCAGTGCTGC TACCAATGCTTAATCAGGGCACCTATCTCAGCGATCTGTCTATTTCGTTCATCCATAGTTG TTTAAATTAAAAGTTTTAAATCAATCTAAAGTATATATGAGTAAACTTGGTCTGACAGT ACGAAAACTCACGTTAAGGGATTTTGGTCATGAGATTTATCAAAAGGATCTTCACCTAGATCCT CGCAGAAAAAAGGATCTTTCTTTGATCTTTTTTTTTTCTACGGGGTCTGACGCTCAGTGGA

Fig. 9G

CCGCGCACATTTCCCCCGAAAGTGCCTCTGACGTCTAAGAAACCATTATTATCATGACATTAA ACTITICACCAGCGITITCTGGGTGAGAAAAAGGGAAAGGCAAAATGCCGCAAAAAGGGAATAA GGGCGACACGGAAATGTTGCTCCTTTCCTTTTTCAATATTTTGAAGCATTTTATCA ACCGCTGTTGAGATCCTATTAACCCACTCGTGCACCCAACTGATCTTCAGCATCTTTT CCTATAAAATAGGCGTATCACGAGGCCCTTTCGTC

Fig. 9H

AGCGTGTCTCCGAGCCCGCTGATGCTACTGCACCCGCCGCCGCAGCTGTCGCCTTTTCCTGCAGC CGGCCCCGGGTTTGCGCTTCCAACGGCCTGGGGGGTTTCCCCCCTTAAC CCTACGAGTTCAACGCCGCCGCCCAACGCCAGGTCTACGGTCAGACCGGCCTCCCTA CCCTGGGCGAGGTGTACCTGGACAGCAAGCCCGCCGTGTACAACTACCGAGGGCCCCG TCAGATCCAAGGGAACGTCCCTGAACCGTCCGCAGCTCAAGATCCCCTGGAGCGG GAATTCCCCCCCCCATGACCCTCCACACCAAAGCATCGGGATGGCTTGCA ACGCCATCCACGCTGTTTTGACCTCCATAGAAGACACCGGGACCGATCCAGCCTCCGCGCCCC GGCGTGTACGGAGGCCCTATATAAGCAGAGCTCGTTTAGTGAACCGTCAGATCGCCTGGAG AGTTTACCACTCCCTATCAGTGAGAAAGTGAAAGTCGAGCTCGGGTCGGGTCGAGTA TGATAGAGAAAAGTCGAGTTTACCACTCCCTATCAGTGATAGAAAAGTGAAAAGTCG CGAGTTTACCACTCCCTATCAGTGAAAAGTGAAAGTCGAGTTTACCACTCCCTATCAG AGTGATAGAGAAAAGTCGAGTTTACCACTCCCTATCAGTGATAGAAAAGTGAAAAGT CTCGAGTTTACCACTCCCTATCAGTGAGAAAAGTGAAAAGTCGAGTTTACCACTCCCTATC

Fig. 10A

ATCAACTGGGCGAAGAGGGTGCCTTTTGTGGATTTGACCCTCCATGATCAGGTCCTTT TAGAATGTGCCTGGCTAGATCCTGATTGGTCTCGTCTGGCGCTCCATGGAGCACCCAGT CTTCAGTGAAGCTTCGATGACGTTACTGACCAACCTGGCAGACAGGGAGCTGGTTCACATG TGGTCATGGCCTTGGATGCCCCCCCATACTCTTTCCGAGTATGATCCTACAGACC AGCCCGCTCATGATCAAACGCTCTAAGAAGAACAGCCTGGCCTTGTCCCTGACGGCCGACCAGA TGATGGGGGGGGGGGGGGGTCTGCTGGAGACATGAGAGCTGCCAACCTTTGGCCA GATAAAAACAGGAAGAAGACTGCCAGGCCTGCCGGCTCCGCAAATGCTACGAAGTGGGAATGA TGAAAGGTGGGATACGAAAAAGACCGAAGAGGAGGAGAATGTTGAAACACACAAGCCCAGAGAGA CTICAAGAGAAGTATICAAGGACATAACGACTATATGIGICCAGCCAACCAGTGCACTIT TACCATTATGGAGTCTGGTGTGAGGGCTGCAAGGCCTT GCCAGTACCAAGGGAAGTATGGCTATGGAATCTGCCAAGGAGACTCGCTACTGCAG CCCACGGCCAGCAGGTGCCCTACCTGGAGAACGAGCCCAGCGGCTACAGGGTGCGAGGC CGGCCCGCCGCCATTCTACAGGCCCAAATTCAGATAATCGACGCCCAGGGCTGGCAGAAAAATTG TGTGCAATGACTATGCTTCAGGC

Fig. 10B

CTTTATTTGTGAAATTTGTGATGCTATTGCTTTATTTGTAACCATTAAGCTGCAATAAACAA ATTTTATGTTTCAGGGGGGGGGTGTGGGGAGGTTTTTT TGCCACAGTCTGAGAGCTCCCTGGCGGAATTCGAGCTCGGGTACCCGGGGATCCTCTAGAGGATC CAGACATGATAAGATACATTGAGTTTGGACAAACCACAACTAGAATGCAGTGAAAAAAATG CATGCGCCCACTAGCCGTGGGGGCATCCGTGGAGGAGGACGACCAAAGCCACTTGGCCACTG TCCTCCTCATCTCCCACATCAGGCACATGAGTAACAAAGGCATGGAGCATCTGTACAGCAT GAAGTGCAAGAACGTGCCCCCTCTATGACCTGCTGGAGATGCTGGACGCCCACCGCCTA AGGAGTTTGTGTGCCTCAAATCTATTTTTGCTTAATTCTGGAGTGTACACATTTCTGTCCAG CACCCTGAAGTCTCTGGAAGAAGGACCATATCCACGAGTCCTGGACAAGATCACAGACACT GTGGAGATCTTCGACATGCTGCTACATCATCTCGGTTCCGCATGATGAATCTGCGGAG GAAGCTACTGTTTGCTCCTAACTTGCTCTTGGACAGGAACCAGGGAAAATGTGTAGAGGGCATG GTTAACAACAACAATTGCATTC

Fig. 10C

CTCTCCTGTTCCGACCCTGCCTTACCGGATACCTGTCCGCCTTTCTCCCTTTCGGGAAGCGTG GGTGGCGAAACCCCGACAACATACCAGGCGTTTCCCCCTGGAAGCTCCTTGGTGCG CTGGCGT. TTTCCATAGGCTCCGCCCCCTGACGAGCATCACAAAATCGACGCTCAAGTCAGA CGCAGGAAAGAACATGTGAGCCAAGGCCAAAAGGCCAGGAACCGTAAAAAGGCCGCGTTTG TGCGGCGAGCGGTTCACTCAAAGGCGGTAATACGGTTATCCACAGAATCAGGGATAA GGTTTGCGTATTGGGCGCTCTTCCTCGCTCACTGACTCGCTGCGCTCGGTCGTTCGGC TCAATGTACCTATAACCAGACCGTTCAGCTGCATTAATGAATCGGCCAACGCGGGGGAGAGGC CGACCAAGCTTGGCGAGATTTTCAGGAGCTAAGGAAAAATGGAGAAAAAATCACTGGAT GAGGCAAGACTCGGGGGGCGCCTGCCGTCCCAGGTCAACAGGCGGTAACCGGCCTCTTC GCCGGACCACGCTATCTGCAAGGTCCCCGGACGCGCGCTCCATGAGCAGAGCCCCCGCCC AAAGCAAGTAAAACCTCTACAAATGTGGTATGGCTGATTATGATCCTGCAAGCCTCGTCGTCTG

Fig. 10D

GGGCCGAGCGCAGAAGTGCTGCAACTTTATCCGCCTCCAAGTCTATTAATTGCCG CCTGATCCCCCGTCGTAGATAACTACGATACGGGAGGGCTTACCATCTGGCCCCAGTGCTGCA TACCAATGCTTAATCAGGGCACCTATCTCAGCGATCTGTCTATTTCGTTCATCCATAGTTG TTTAAATTAAAAGTTTTAAATCAATCTAAGTATATATGAGTAAACTTGGTCTGACAGT CGCAGAAAAAAAGGATCTCTTTGATCTTTTTTTTTTCTACGGGTCTGACGCTCAGTGGA TIGGICATGAGATTATCAAAAAGGATCTTCACCTAGATCCT GGACAGTATTTGGTATCTGCTCTGCTGAAGCCAGTTACCTTCGGAAAAAAGAGTTGGTAGCTC GCGAGGTATGTAGGCGGTGCTACAGAGTTCTTGAAGTGGTGGCCTAACTACGGCTACACTAGAA GTCCAACCCGGTAAGACACGTTATCGCCACTGGCAGCCACTGGTAACAGGATTAGCAGA GCTGTGTGCACGAACCCCCCGTTCAGCCCGACCGCTGCGCCTTATCCGGTAACTATCGTCTTGA GCGCTTTCTCAATGCTCACGCTGTAGGTATCTCAGTTCGGTGTAGGTCGTTCGCTCCAAGCTGG ACGAAAACTCACGTTAAGGGATT

Fig. 10E

DRAFIS:

GGTTATTGTCTCATGAGCGGATACATATTTTGAATGTATTTTAGAAAAATAAAAAATAGGGGGTTC CGCGCACATTTCCCCGAAAAGTGCCTCCTGACGTCTAAGAAACCATTATTATCATGACATTAAC GGCGACACGGAAATGTTGCTCCTCTTCCTTTTTCAATATTTGAAGCATTTTATCAG CCGCTGTTGAGATCCTGATCTCGTCTCGTGCACCCAACTGATCTTCAGCATCTTTAA CTTTCACCAGCGTTGGGCAAAAACAGGAAGGCAAAATGCCGCAAAAAAAGGGAATAAG AGTGTATGCGGCGACCCGACTCTTGCCCCGGCGTCAATACGGGATAATACCGCCCCACATAG GTCATGCCATCCGTAAGATGCTTTTTCTGACTGGTGAGTACTCAACCAAGTCATTCTGAGAAT CAGAAGTAAGTTGGCCGCAGTGTTATCACTCATTGGTTATGGCAGCACTGCATAATTCTTTATACT GAGTTACATGATCCCCCCATGTTGCAAAAAGCGGTTAGCTCCTTCGGTCCTCCGATCGTTGT ATCGTGGTGTCACGCTCGTTTGGTATGGCTTCATTCAGCTCCGGTTCCCAACGATCAAGGC GGAAGCTPGAGTAGTTCGCCAGTTAATAGTTTGCGCAACGTTGTTGCCATTGCTACAGGC CTATAAAAATAGGCGTATCACGAGGCCCTTTCGTC

Fig. 10F

F16.11

GUJCLASS

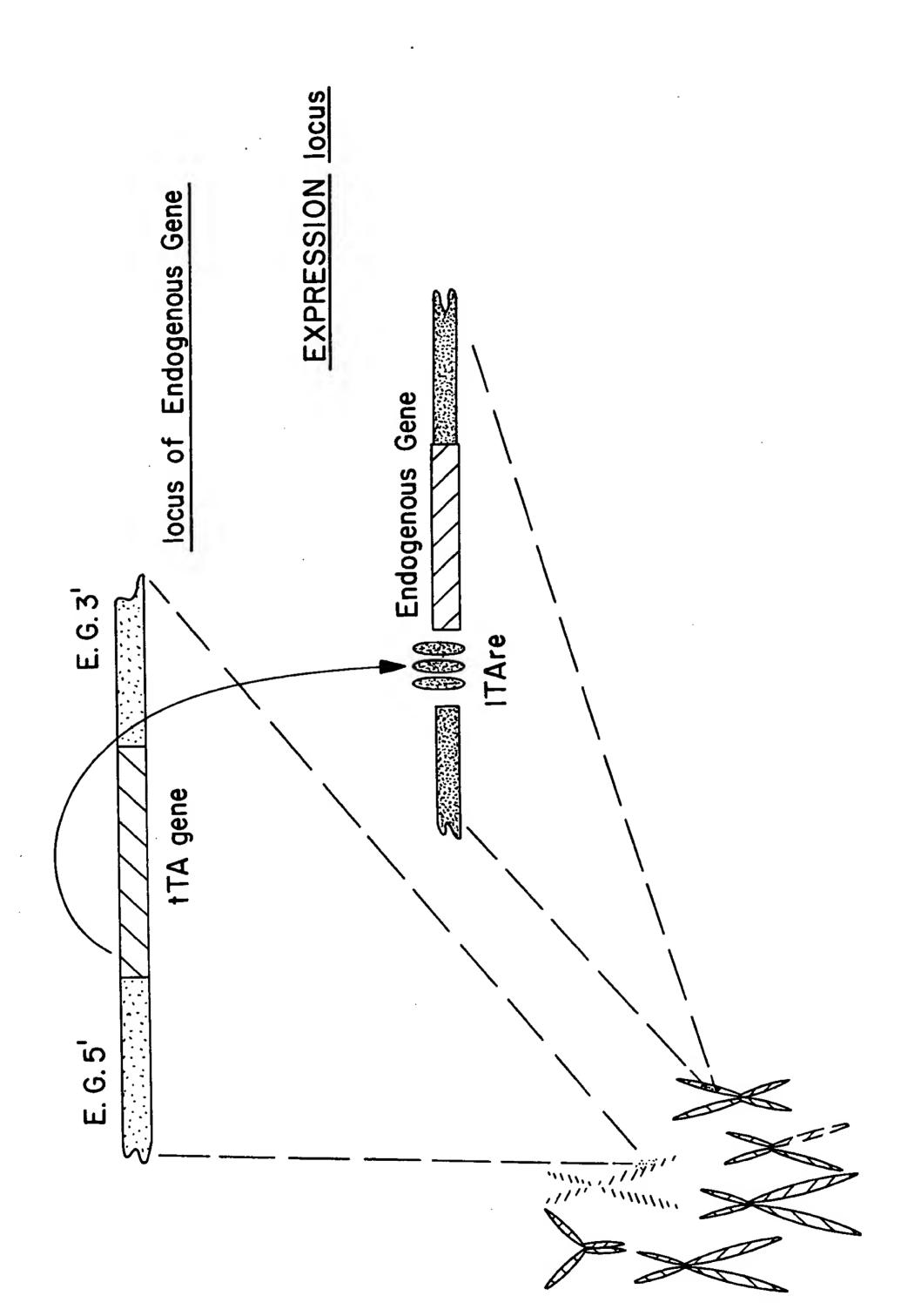
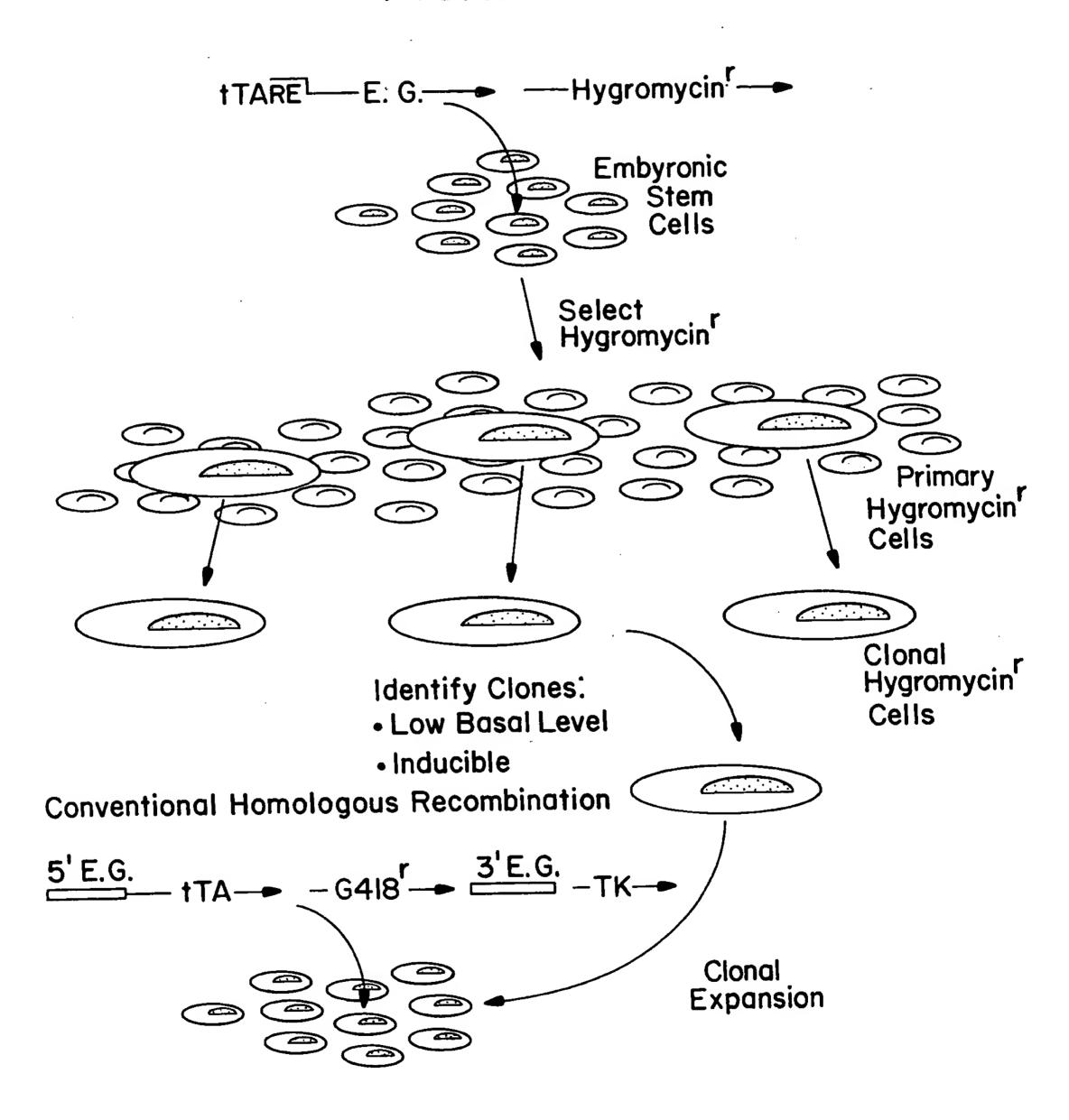
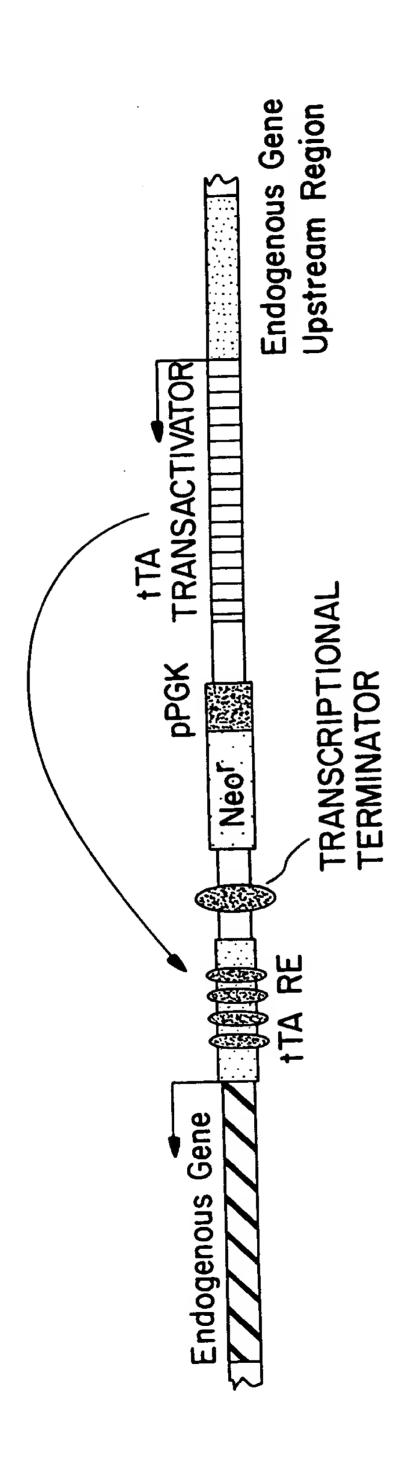


FIG. 12

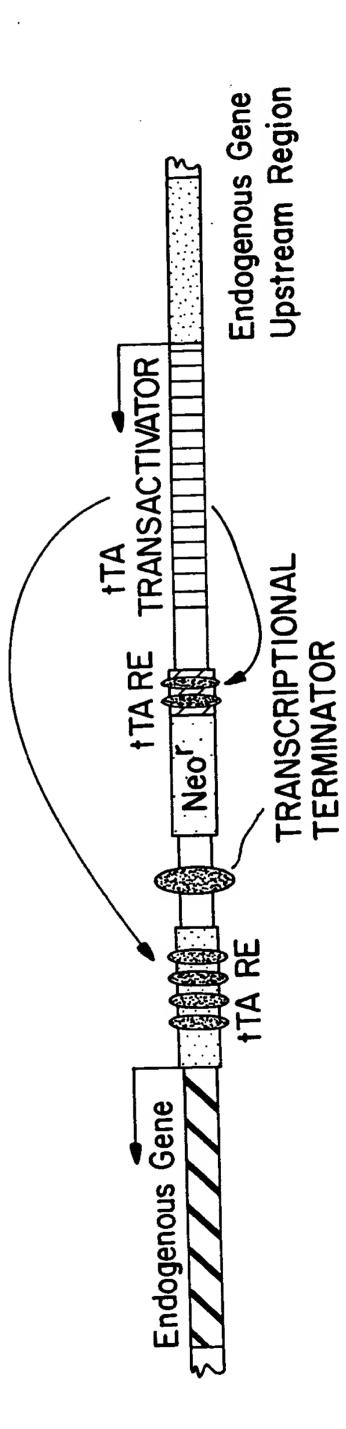


F16.13A

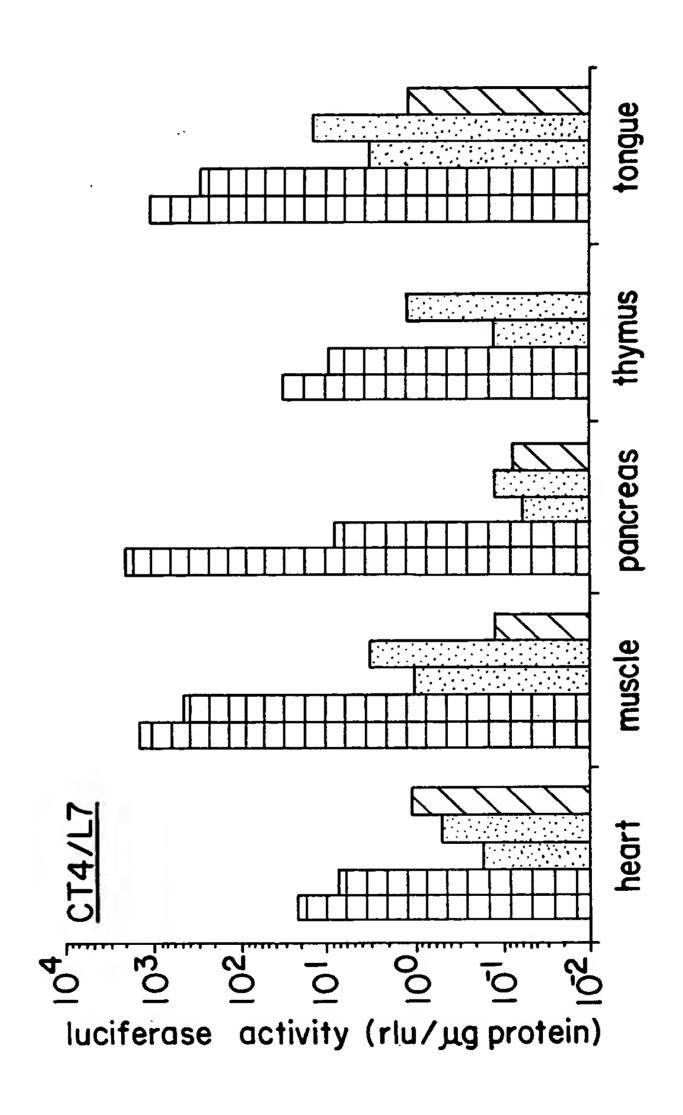
NO.



F1G. 13B



F16.14



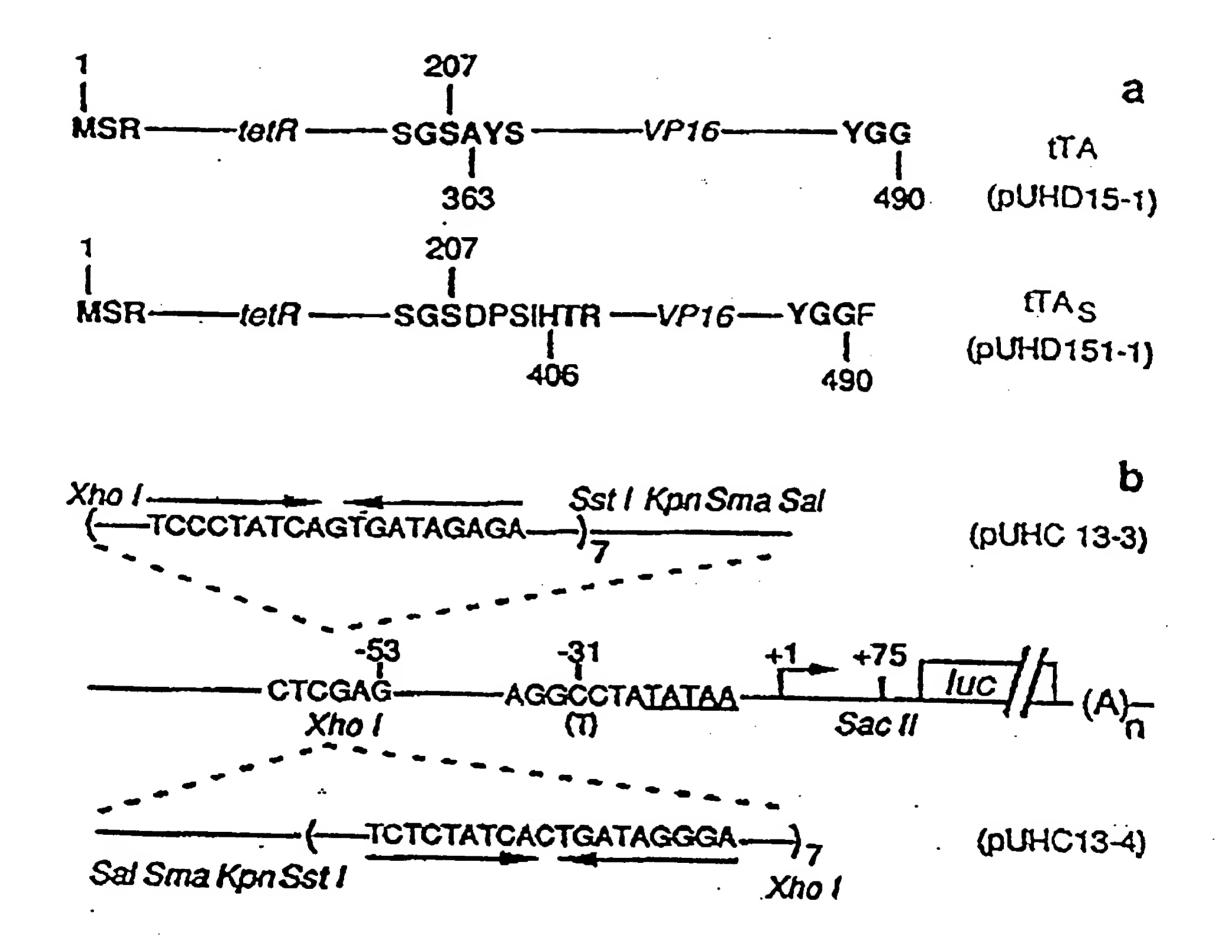


Fig. 1

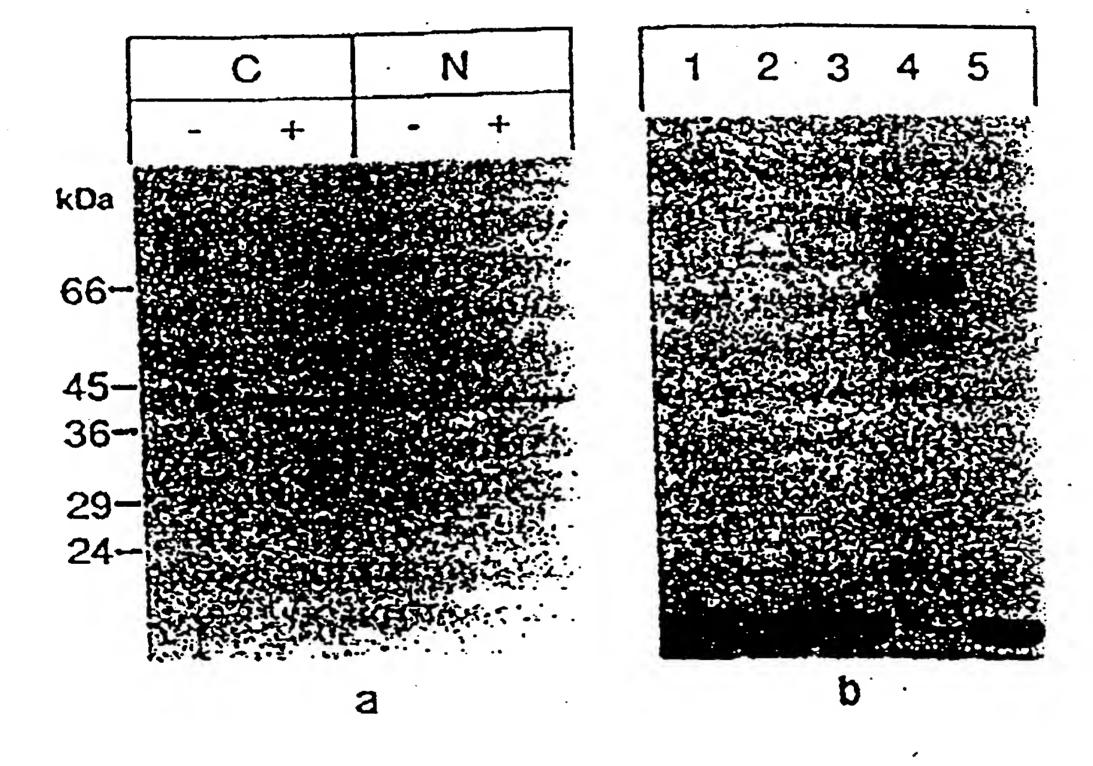


Fig. 2

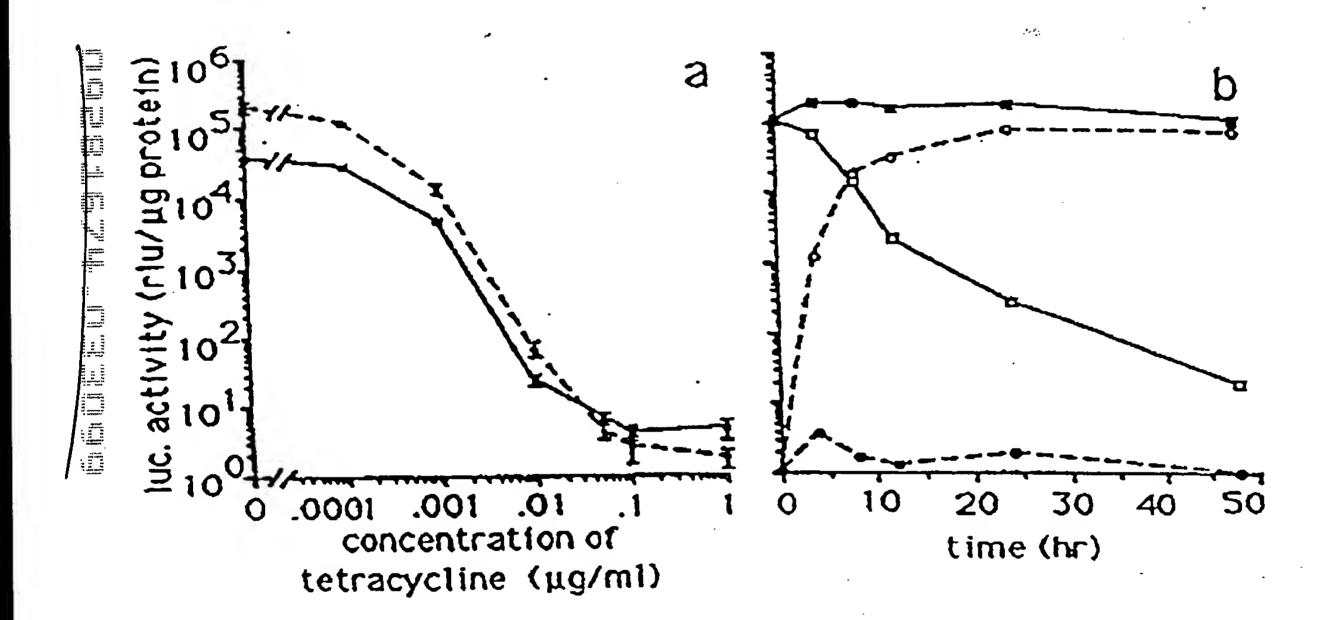


Fig. 3

31/11 ATG TOT AGA TEX GAT ANA AGT ANA GTG ATT AND AGC GCA TEX GAG CTG CTT ANT GAG GTC 1/1 Met ser ary leu asp lys ser lys val ile asm ser ala leu glu leu asm glu val 91/31 51/21 GGR ATC GAR GGT TEX ACA ACC CGT AAA CTC GCC CAG AAG CTA GGT GEA GAG CAG CCT ACA gly the glu gly len thr thr arg lys len ala gln lys len gly val glu glu pro thr 151/51 121/41 TTG TAT TOG CAT GIR AAA AAT AAG COG GCT TTG CTC CAC CCC TTA GCC ATT CAG ATG TTA leu tyr tro his val lys asn lys ary ala leu leu asp als leu ala ile glu met leu 211/71 181/61 CAT AGG CAC CAT ACT CAC TIT TOO OCT TIA GAA GGG GAA AGC TOG CAA CAT TIT TIA CCT amp and his his the his phe cys pro leu glu gly glu ser trp glu amp phe leu and 271/91 241/81 ANT ANG COT AND AGT TIT AGA TOT COT TITA CITA AGT CAT CGC GAT GGA GCA ANA CITA CAT ann lys ala lys ser phe arg cys als less less ear his arg asp gly ala lys val his 331/111 301/101 TIN GGT ACA CGG CCT ACA GAA AAA CAG TAT GAA ACT CTC GAA AAT CAA TIA GCC TTT TTA led gly the arg pro the glu lys gla tyr glu the led glu sen gla led als phe led 391/131 361/121 TOC CAA CAA GGT TTT TCA CTA CAG AAT GCA TIA TAT GCA CTC AGC GCT OTG GGG CAT TIT oye gin gin gly phe ser leu giu aen sia leu tyr ala leu ser ala val gly his phe 491/151 421/141 ACT THE OCT TOC OTA TTO CAR CAT CAR CAE CAT CAR OTC GCT AND CAR CAR AGE CAR ACE thr leu gly eye wal leu glu asp gln glu his gln wal sla lys glu glu arg glu thr \$11/171 481/161 OCT ACT ACT GAT AGT ATG COG OCA TEA TEA OGA CHA OCT ATC GAR TEA TET GAT CAC CAA pro thr the asp ser met pro pro leu leu ary glo ala ile giu leu phe aep his glo 571/191 541/181 GGT GCA GAG GCA GCC TTC TTA TTC GGC CTT GAA TTG ATC ATA TGC GGA TTA GAA AAA GAA gly ala glu pro ala phe leu phe gly leu glu leu ile ile cys gly leu glu lys gla 631/211 601/201 CIT AND TOT GAD ACT OCCUTED COO THE ACC COC CCC CCC ACC AND AND AND THE GOO TOT led lys cys glu ser gly ser ale tyr ser ary ala ary thr lys ann ann tyr gly car 691/231 661/221 thr ile glu gly leu leu amp leu pro amp amp amp ala pro glu glu ala gly leu ala 751/251 721/241 OCT COG CGC CTG TOC TIT CTC COC GCG GGA CAC ACG CGC ACA CTG TCG ACG GCC CCC CCG ala pro ary leu ser phe leu pro ala gly his thr ary ary leu ser thr ala pro pro 811/271 781/261 ACC CAT GIC AGC CIG GGG GAC GAG CIC CAC TITA GAC GGC GAG GAC GTG GCG ATC GCG CAT thr asp wal ser led gly sap glu led his led asp gly gld asp wal als met als his 871/291 841/281 QCC CAC CCC CIA GAC CAT TIC GAT CIG CAC ATC TIG CEG CAC GGG GAT TCC CCG GGT CCC als asp als led seb seb bue sab led seb met led gly seb gly sab ser bro gly pro 931/311 901/301 GGA TIT ACC COC CAC GAC TOC GCC CCC TAC GCC GCT CTG GAT ATG GCC GAC TTC GAC TTT gly phe thr pro his sep cer als pro tyr gly als leu sep met als sep phe glu phe 991/331 961/321 GAG CAG ATG TIT ACC GAT COC CIT GGA ATT CAC CAG TAC GGT GGG TAG glu gln met phe thr sep pro leu gly ile asp glu tyr gly gly AMB

31/11 AND TET AGA TEA GAT AAA AGT AAA GTG ATT AAC AGE GCA TEA GAG CTG CTF AAT GAG GTC Not ser ary lau asp lys ser lys val 11e sen ser ala leu glu leu leu esn glu val 91/31 GGA ATC CAA GOT THE ACA ACC CUT ALL CTC CCC CAG ANG CTA CCT GTA CAG CAG CCT ACA 61/21 gly ile glu gly leu thr thr are lys leu ala gln lys leu gly val glu gln pro thr 151/51 121/41 TIG TAT TGG CAT GIA AAA AAT AAG COG OCT TIG CIC CAC GOC TIA GOC AIT GAG ATG TIA lou tyr trp his val lys asm lys arm ala leu leu asp ala leu ala ile glu met leu 211/71 181/51 GAT AGG CAC CAT ACT CAC TIT TGC CCT TIA GAA GGG GAA AGC TGG CAA GAI TIT TIA CCT map any his his the his phe cys pro leu gla gly glu eer tro gln asp pha leu arg 271/91 241/01 ANT AND GOT ANA NOT TIT AGA TOT COT TIL CTA NOT CAT COD ONT COA OCA ANA CTA CAT ach ash ala lys ser phe any cys ala leu leu ser his arg asp gly ala lys wal his 331/111 301/101 TTA GGT ACA CGG CCT ACA CAA AAA CAG TAF CAA ACT CTC CAA AAT CAA TTA GCC TTT TTA led gly thr are pro thr glu lys gln tyr glu thr led glu asn gln led als phe lod 391/131 361/121 TOC CAA CAA GOT TIT TOA CEA GAG AAT GOA TIA TAT GOA CTC AGC GOT GTG GGG CAT TIT cys gla gla gly phe ser leu glu am sla leu tyr ala leu ser sla vel gly his phe 451/151 421/141 ACT TIN GOT TOO OIR TIC CAR CAT CAR CAG CAT CAR GIC GCT ARA GAR GAR AGG GAR ACA thr leu gly cys wal leu glu asp gla glu his gla wal ala lys glu glu erg glu thr 511/171 481/161 COT ACT ACT GAT AGT ATG COG COA TTA TTA COA CAA GOT ATC GAA TTA TTT GAT CAC CAA pro thr thr asp ser met pro pro leu leu arg gin ala ile glu leu phe asp his gin 571/191 541/181 OCT OCA CAG OCA OCC TTC TICA TTC OCC CTT CAA TTC ATC ATA TOC GGA TTA CAA AAA CAA gly ala glu pro ala phe Leu phe gly leu glu leu ile ile cye gly leu glu lye gla 631/211 601/201 CTT AND TOT GAD AND GOOD TOT GAT OCK TOO ATA CAN MOS GOO AGA CITS TOO ACE GOO COO leu lys cys glu ser gly ser asp pro ser ile his thr ary arg leu ser thr ala pro 691/231 661/221 COOR AND CART GTC AGC CTG GGG GAC GAG CTC CAC TEA GAC GGG GAG GAC GTG GCG ATG GCG pro thr amp wal ser leu gly amp glu leu his leu amp gly glu amp wal ala met ala 751/25% 721/241 CAT GOO GAC GOG CTA GAC GAT TTC GAT CTC CAC ATC TTG GOG GAC GGG GAT TCC CCC GGT his als asp als led seb asp bye sab led sab mat led dly sab dly seb ser bro dly 811/271 781/261 COS GGA TIT ACC COC CAC GAC TOC GCC CUT TAC GGC GCT CTG GAT ATG GCC GAC TTC CAG pro gly phe thr pro his sep ser als pro tyr gly als leu asp met als asp phe glu 871/291 841/281 TIT GAG CAG ATG TIT ACC GAT GCC CIT GGA ATT GAC GAG TAC OCT GGC TIC TAC phe glu gla met phe thr asp ala leu gly ile asp glu tyr gly gly phe AMB

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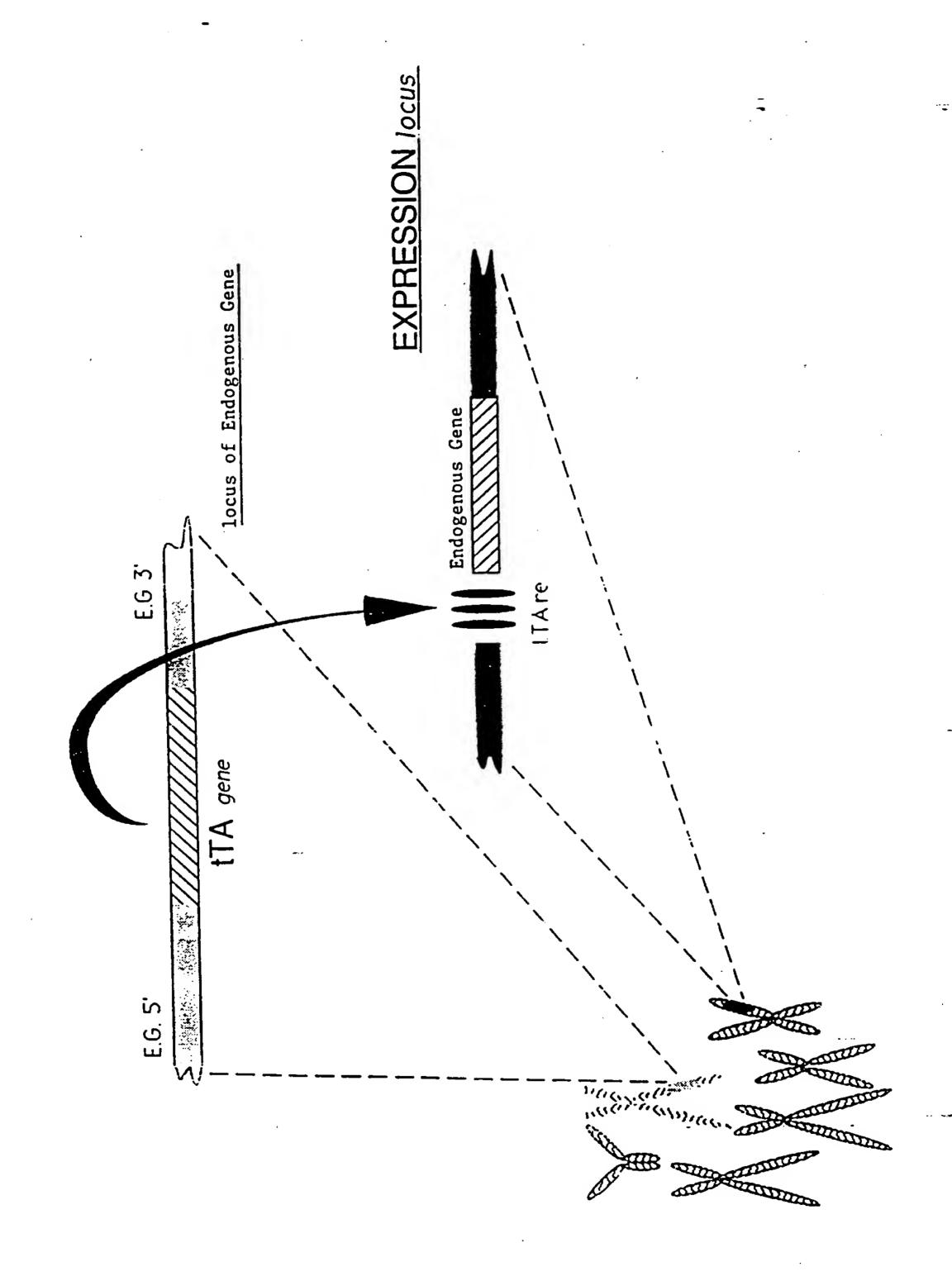
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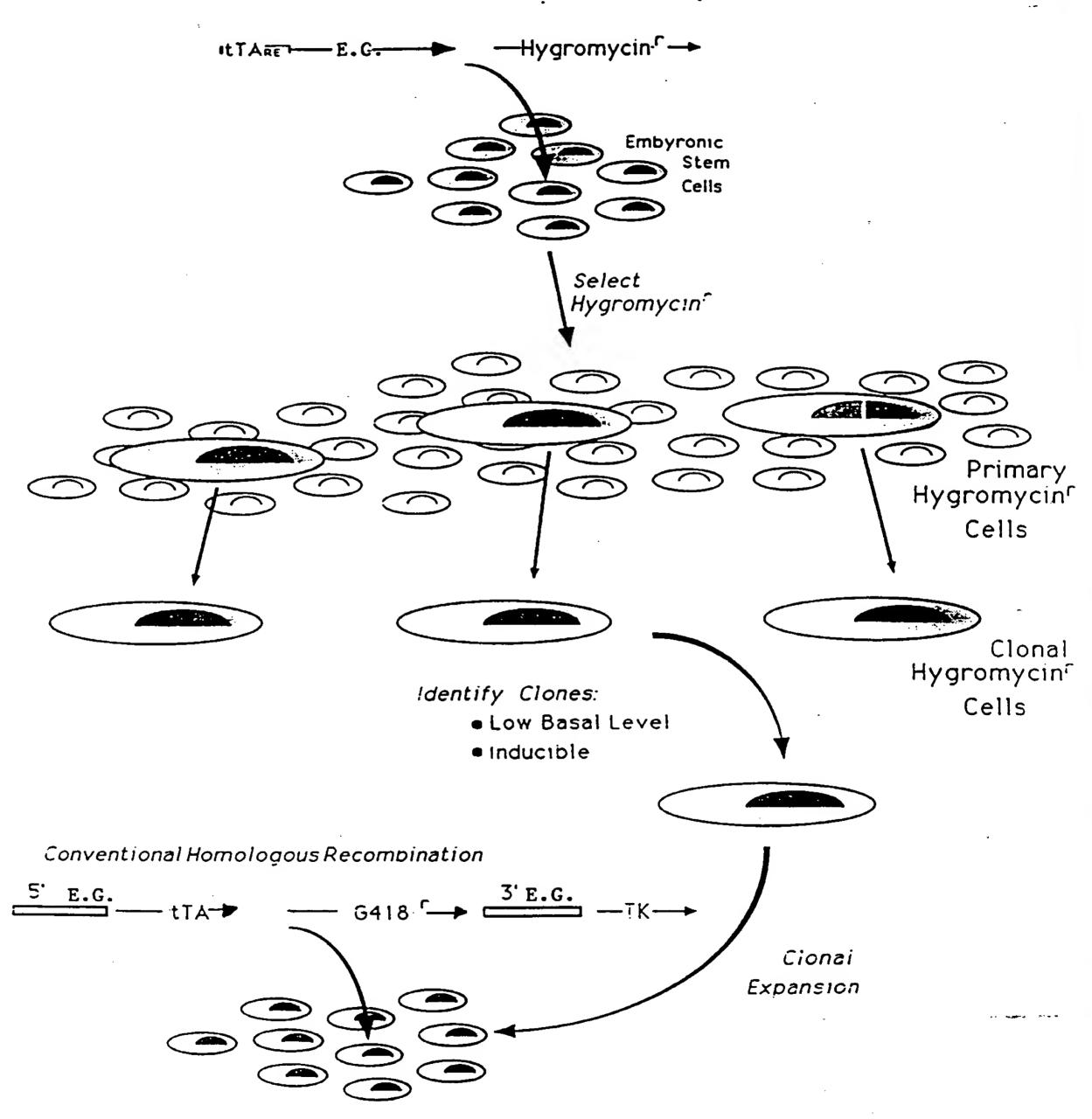
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Conditional Knock-Out Strategy 1



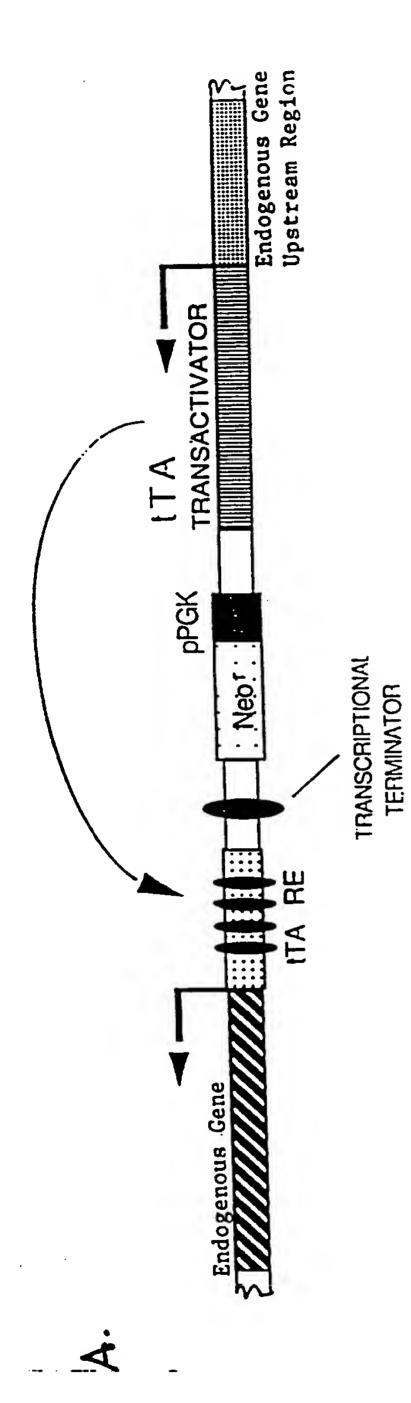
Conditional Knock-Out Strategy 2

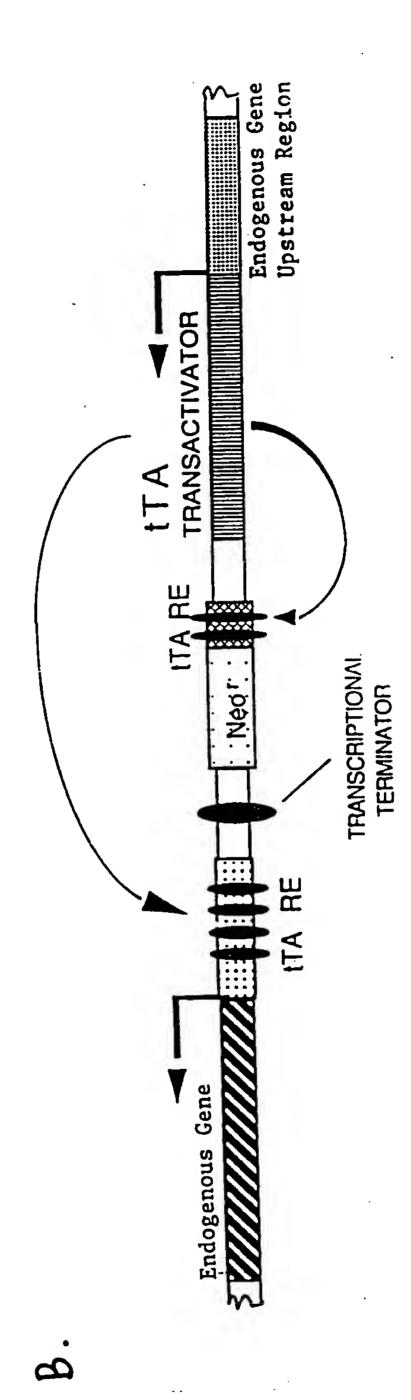


Identify clones with low basal activity of endogenous gene (near untransformed levels). Identify among these those which respond to tTA (by transient expression).

Perform homologous recombination into endogenous locus.

Conditional Knock-Out Strategy 3





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Figure 14